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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/577,840	02/01/2007	Pere Joan Cardona Iglesias	TJA-139US	9930

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EXAMINER	
LI, QIAN JANICE	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/577,840	CARDONA IGLESIAS ET AL.	
	Examiner	Art Unit	
	Q. JANICE LI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4/13/2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-19,21-27,35-37 and 44-60* is/are pending in the application.

4a) Of the above claim(s) *13-19,21-27,35-37 and 44-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment and remarks filed 4/13/2011 are acknowledged. Claim 47 has been amended. Claims 47-60 are under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. The arguments in 4/13/11 response would be addressed to the extent that they apply to current rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 47-49, 51-55 stand rejected under 35 U.S.C. 103(a) as obvious over *Kumazawa et al.* (Japan J Microbiol 1976;20:183-190) in view of *Ragland* (USP 4,744,984), for reasons of record and following.

Kumazawa teaches a pharmaceutical composition comprising cell wall fragments from virulent *Mycobacterium tuberculosis* strain Aoyama B (see e.g. the abstract). *Kumazawa* teaches culturing the MTB-C for 8 weeks, which were then killed by heating, thoroughly washed, delipidated with acetone and chloroformmethanol, hydrogenolyzed in ethanol containing 20% acetone, which homogenized the bacterial cells and then the water-soluble extracts were lyophilized and gel-filtrated with Sephadex G-100 column (see e.g. column 1, page 184). When used as an adjuvant, *Kumazawa* teaches the MTB-C fraction was dissolved in saline (neutral pH). Although not mentioned, PBS buffer was the most commonly used alternative to saline.

The teaching of *Kumazawa* differs from instant claims only in that the non-ionic surfactant was absent from the homogenizing process.

Ragland supplemented *Kumazawa* by establishing it was well known in the art to prepare mycobacteria wall extract using nonionic surfactant such as triton X-100 (an octylphenol ethoxylate compound). *Ragland* teaches a process for preparing a modified mycobacteria cell wall composition as a pharmaceutical agent (e.g. the abstract), wherein the process comprises culturing the bacteria for 10-20 days, disrupting the bacterial cells by either pressure or sonic energy, which released soluble cell components from the bacterial cells, collecting disrupted cell walls by washing, centrifugation and re-suspending cell wall fragments in distilled water. The cell wall fraction is then washed and separated from any unbroken cells (e.g. columns 4-5). *Ragland* went on to teach optionally the cell wall fraction was further treated with detergent such as Triton X-100 and lyophilized (column 5, lines 22-41). Although *Ragland* does not specifically teach the reasoning for using detergent treatment, it was well known in the art that detergent serves as an alternative or additional measure for physical disruption of bacterial cell wall.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the composition as taught by *Kumazawa* by including the optional Triton X-100 detergent treatment as taught by *Ragland* with a reasonable expectation of success. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

In the remarks, the applicant first explains the claimed immunotherapeutic agent obtained according to the stated method shows an unexpected synergism for treating tuberculosis when combined with other drugs and argues the effect of the synergy was not predictable from the cited prior art documents.

Applicant's arguments filed 4/13/2011 have been fully considered but they are not persuasive. This is because the claims under examination are directed to a composition, not a process of treating tuberculosis. Hence, the stated unexpected result from the combination does not apply to the claimed composition, for which the novelty of the MTB-C cell wall fragments is determined by the structural features.

The applicant then argues that *Kumazava* discloses the preparation of a water-soluble adjuvant whereas present immunotherapeutic agent comprising cell wall

fragments, which are insoluble in water. The applicant asserts claim 47 makes clear that the immunotherapeutic agent corresponds to the non-solubilized cell wall fragments.

The argument has been fully considered but found not sufficient to obviate this rejection. This is because the teaching of *Kumazava* was not limited to the illustrated embodiment and claim 47 embraces both water-soluble and water-insoluble cell wall extracts. The preparation in *Kumazava* was water-soluble extract of the lysed whole cell, hence including fractions of cell wall. Step c of claim 47 states separating the cell wall fragments (including soluble and insoluble ones) from the non-fragmented cells and the solubilized cell compounds, but the claims do not contain a limitation wherein only the water-insoluble cell wall fragments are present in the composition. Hence, the claimed agent embraces the water-soluble cell wall fragment disclosed by the combined teaching.

The applicant then asserts that the adjuvant obtained by *Kumazava* does not contain cell wall fragments but water extracts from hydrogenolyzed cells, i.e. chemically modified cells.

In response, again *Kumazava* obtained water-soluble extract from a hydrogenolyzed whole cell including solubilized cell wall fragments and clearly indicated that the cell wall of mycobacteria is a peptideoglycan linked to mycolic acid and contained in the MAF3 adjuvant. *Kumazava* acknowledges the MAF3 appears to contain components from both the cell wall and the cytoplasm (see page 189).

More importantly, the teaching of *Kumazava* was not limited to the exemplified water-soluble bacterial wall adjuvant. In the introduction, *Kumazava* reviewed published

literatures discussing bacterial wall preparation, and clearly illustrated the state of the prior art concerning mycobacterial cell wall preparation and other means in the art to make immunotherapeutic agent comprising purified mycobacterium cell walls such as those cited (see e.g. page 183). From the discussions, it is apparent that *Kumazava* was preparing a composition, wherein predominant component was bacterial cell walls. In the newly submitted evidence B by the applicant, both the datasheet of TB vaccine cell wall preparation and the cited reference within of *Hirschfield* are specifically directed to preparing insoluble mycobacterial cell walls.

The applicant then listed a comparison table showing how the process of example 1 differs from that of *Kumazava,* and argues hydrogenolysis differs from homogenization.

The argument has been fully considered but found not sufficient to obviate this rejection. This is because **a**). the claimed process is broader than example 1, and the rejection is not solely relied on the exemplified embodiment of *Kumazava*; **b**). the limitation of "insoluble cell wall fragments" is not in the current claim; **c**). the rejection is not a 35 U.S.C. 102 rejection, but relies on the combined teachings. To this end, the applicant is reminded it was *Ragland* who illustrates making bacterial cell wall preparations by homogenization, and separating the cell wall fragments from the non-fragmented cells, wherein both insoluble and soluble cell wall fractions were discussed, wherein non-ionic surfactant was used (e.g. columns 4-6, also see previous rejections *supra*).

The applicant then argues that there is no hint in *Kumazava* that the adjuvant is for treating tuberculosis. The argument is not persuasive because the claims are directed to a composition, not a method of treating tuberculosis. The intended use limitation carries little weight in a product claim and the recited limitation "cell wall fragments from a virulent *Mycobacterium tuberculosis*-complex strain of cells" is met by the combined teachings.

With regard to *Ragland*, the applicant raised three points:

1). "It does not disclose a virulent strain of MTB-C". In response, *Kumazava* remedied the deficiency.

2). "The preparation was used by *Ragland* for antiviral features, not treating tuberculosis". In response, "treating tuberculosis" is not part of the recited claim limitation. Further the applicant is reminded that the use of a product for a particular purpose is not afforded patentable weight in a product claim where the body of the claim does not depend on the preamble for completeness but, instead, the structural limitations are able to stand alone. The MPEP states "in apparatus, article, and composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art." In re Casey, 152 USPQ 235 (CCPA 1967); In re Otto , 136 USPQ 458, 459 (CCPA 1963)(MPEP 2111.02).

3). "The applicant claimed agent is suitable for the treatment of tuberculosis and shows synergism when combined with other drugs". In response, the claims are directed to a product, not a process claim. If the structure taught by the combined

teachings met the structural limitation of the claims, it would be capable of performing the intended use. In this case, *Ragland* used the preparation for its non-specific immunostimulatory property, however, as indicated *supra*, in view of the state of the art as a whole, the teaching of *Kumazava*, it appears all the recited elements were known in the art, and hence "the combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR*, 127 S. Ct. at 1740, 82 USPQ2d at 1395-96. Accordingly, it would have been obvious to the skilled in the art to prepare an immunogenic agent comprising a cell wall fragment from a virulent strain of MTB-C having either or both soluble and insoluble fraction(s) using the methods taught by either *Kumazava* or *Ragland* with a reasonable expectation of success.

Regarding previously submitted declaration by the applicant Dr. Cardona, it is noted the declaration was set out to address a rejection relied on completely different prior art. It is also noted most of the arguments are devoted to the effects of the claimed agent on treating tuberculosis, whereas instant claims are directed to a product, wherein the novelty was determined by the structural component.

Accordingly, for reasons of record and set forth *supra*, the claimed invention as a whole was *prima facie* obvious.

Claim 50 stands rejected under 35 U.S.C. 103(a) as obvious over *Kumazawa et al.* (Japan J Microbiol 1976;20:183-190) in view of *Ragland* (USP 4,744,984) as applied

to claims 47-49, 51-55 above, further in view of *Mohr et al.* (USP 7,214,651), for reasons of record and following.

The combined teaching of *Kumazawa* in view of *Ragland* does not mention the ethylene oxide (EO) content of the ethoxylates.

Mohr supplemented *Kumazawa* in view of *Ragland*. *Mohr* teaches that ethoxylates having 5-7 or more than 7 EO units are effective disinfectant for disinfection against mycobacterium (e.g. claims 1 and 14).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the composition as taught by *Kumazawa* in view of *Ragland* by using the 7-8 mol EO triton X-100 surfactant with a reasonable expectation of success for disinfection of mycobacterial cell walls. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

In the remarks, the applicant argues according to *Mohr*, the disclosed composition is suitable for disinfect hard surfaces, not for preparing virulent strain of MTB-C as instantly claimed.

Applicant's arguments have been fully considered but they are not persuasive. It is noted the *Mohr* patent is titled "*Disinfectant having improved activity against mycobacteria*". Accordingly, it would have been obvious for an ordinary skilled to use the improved disinfectant for disinfecting/inactivating virulent strain of mycobacterial cells whenever such need arises.

Accordingly, for reasons of record and set forth *supra*, the rejection stands.

Claims 47-49, 51-55 stand rejected under 35 U.S.C. 103(a) as obvious over *Kumazawa et al.* (Japan J Microbiol 1976;20:183-190) in view of *Ragland* (USP

4,744,984) and further in view of *Lyons et al.* (Infect Immunity 2002; 70:5471-8), for reasons of record and following.

Kumazawa in view of *Ragland* do not specifically teach the elected virulent strain H37Rv.

Lyons supplemented the combined teaching by establishing it was well known in the art the cell wall extract of *Mycobacteria* strain H37Rv had been used as a vaccine composition for treating *Mycobacterium tuberculosis* infection (see e.g. column 1, page 5472 and figure 4).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use either the *Mycobacterium tuberculosis* strain Aoyama B as taught by *Kumazawa* or strain H37Rv as taught by *Lyons* with a reasonable expectation of success. Given the knowledge of the skilled, the limitation falls within bounds of optimization. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

In the remarks, the applicant argues *Lyons*'s composition was likely prepared by a different process and provided a reference and product datasheet and a table for comparison and support of arguments.

Applicant's arguments have been fully considered but they are not persuasive. This is because the rejection is based on combined teachings. *Lyons* was relied upon providing evidence that the elected species, a specific strain of MTB was well known in the art. It is also noted that the element underlined by the applicant, "*Cells homogenized in the presence of a non-ionic surfactant*" was taught by *Ragland*.

Accordingly, for reasons of record and set forth *supra*, the rejection stands.

Claim 56 stands rejected under 35 U.S.C. 103(a) as obvious over *Kumazawa et al.* (Japan J Microbiol 1976;20:183-190) in view of *Ragland* (USP 4,744,984) as applied

to claims 47-49, 51-55 above, and further in view of *Dhiman et al.* (Indian J Exp Biol 1999; 37:1157-66).

Kumazawa in view of *Ragland* do not specifically teach to include liposome in the composition.

Dhiman supplemented the combined teaching by establishing it was well known in the art that liposome may be present in the mycobacteria cell wall composition as an adjuvant (e.g. see table 4).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include liposome in the composition of mycobacterial cell wall extracts with a reasonable expectation of success. Given the knowledge of the skilled, the limitation falls within bounds of optimization. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

In the remarks, the applicant argues *Dhiman* discloses that a cell wall composition in liposome shows a lower efficiency compared with the standard BCG, hence the skilled person would not have been prompted to use cell wall fragments in liposome.

Applicant's arguments have been fully considered but they are not persuasive. This is because *Dhiman* reviews antibtuberculous vaccine and the fact is the skilled had used cell wall fragment in liposome for vaccine before instant priority date as shown by *Dhiman*, hence the limitation is not a novel concept. As to the efficiency, it is a separate issue. Liposome is a drug delivery vehicle, there may be times, one would use liposome to deliver an insoluble composition even though it was less efficient than BCG for other reasons, such as the antigenic diversity of the cell wall fragment. Moreover, the lower efficiency by comparison is not a negation of the use. It is noted the applicant has not reported a comparison to BCG and hence did not establish that the instant claimed

composition is more efficient than BCG vaccine. Accordingly, for reasons of record and set forth *supra*, the rejection stands.

Claims 57-60 stand rejected under 35 U.S.C. 103(a) as obvious over *Kumazawa et al.* (Japan J Microbiol 1976;20:183-190) in view of *Ragland* (USP 4,744,984) and *Dhiman et al.* (Indian J Exp Biol 1999; 37:1157-66) as applied to claims 47-49, 51-56 above, and further in view of *Parikh* (USP 5,785,975).

The combined teachings *supra* did not specify the components of liposome, such as phospholipids and sterols or including Vitamin E in the vaccine composition.

Parikh supplemented the combined teaching by establishing it was known in the art liposome had many forms and components including sterols, phosphatidylcholine, and a bacteria vaccine composition may comprise phophatidylcholine liposome and vitamin E (e.g. claims 10-15, example II, and column 6).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include additional elements in the composition of mycobacterial cell wall extracts with a reasonable expectation of success, wherein the liposome may be phospholipids or sterols, wherein the formulation may comprise vitamin E. Given the knowledge of the skilled, the limitations fall within bounds of optimization. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

In the remarks, the applicant argues *Parikh* does not cue the deficiency of *Kumazawa* and *Ragland*.

In response, for reasons of record and set forth *supra*, the rejection stands.

No claim is allowed.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. JANICE LI** whose telephone number is **571-272-0730**. The examiner can normally be reached on 9 AM -7:00pm, Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

For all other customer support, please call the USPTO Call Center (UCC) at **800-786-9199**.

/Q. JANICE LI/
Primary Examiner, Art Unit 1633